# EXHIBIT 24

AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 131, No. 3


# THE ASSOCIATION BETWEEN HEAD TRAUMA AND ALZHEIMER'S DISEASE

AMY BORENSTEIN GRAVES,[1] EMILY WHITE,[2] THOMAS D. KOEPSELL,[3] BURTON V. REIFLER,[4] GERALD VAN BELLE,[5] ERIC B. LARSON,[6] AND MURRAY RASKIND[7]

**Graves, A. B. (Battelle Seattle Research Center, Seattle, WA 98105), E. White, T. D. Koepsell, B. V. Reifler, G. van Belle, E. B. Larson, and M. Raskind. The association between head trauma and Alzheimer's disease. *Am J Epidemiol* 1990; 131:491–501.**

**The relation between head trauma and Alzheimer's disease was one of four major risk factors explored in a case-control study of 130 matched pairs; cases were clinically diagnosed between January 1980 and June 1985 at two geriatric psychiatric clinics in Seattle, Washington, and controls were friends or nonblood relatives of the cases. Subjects were matched by age, sex, and relationship between the case and his or her surrogate respondent. Head injuries which resulted in a loss of consciousness or which caused the subject to seek medical care were documented by means of interviews with surrogate respondents. A history of head injury was recorded for 24% of the cases and 8.5% of the controls, yielding an odds ratio of 3.5 (95% confidence interval 1.5–8.3) in conditional logistic regression analysis adjusted for age at onset of disease symptoms and family history of Alzheimer's disease. The estimated risk of Alzheimer's disease increased as the time between the last head trauma event and the onset of disease symptoms diminished ($p = 0.002$). This trend remained statistically significant ($p = 0.006$) when head injuries which occurred within 5 years of onset of the disease were excluded from the analysis. There was some difference between cases and controls for the average duration of unconsciousness in events accompanied by such a loss, but this was not statistically significant. The two groups were also similar in the circumstances surrounding the injuries and in the frequency of alcohol problems. This is the third case-control study to find a statistically significant association between head trauma and Alzheimer's disease.**

**Alzheimer's disease; head injuries**

In case reports, dementia has been observed to follow a single injury to the head (1–3). Repeated blows to the head, as experienced by professional boxers, have been associated with dementia pugilistica (4–9), a form of dementia characterized patholog-

Received for publication February 28, 1989, and in final form August 25, 1989.

[1] Battelle Seattle Research Center, Seattle, WA.
[2] Department of Epidemiology, University of Washington, School of Public Health and Community Medicine, Seattle, WA.
[3] Departments of Epidemiology and Health Services, University of Washington, School of Public Health and Community Medicine, Seattle, WA.
[4] Department of Psychiatry and Behavioral Medicine, Bowman Gray School of Medicine, Winston-Salem, NC.
[5] Department of Biostatistics, University of Washington, School of Public Health and Community Medicine, Seattle, WA.
[6] Department of Medicine, University of Washington, School of Medicine, Seattle, WA.
[7] Department of Psychiatry and Behavioral Sciences, University of Washington, School of Medicine, Seattle, WA.

ically by neurofibrillary tangle formation in the absence of neuritic plaques (10), both of which are commonly observed in Alzheimer's disease. Of eight epidemiologic studies of Alzheimer's disease (11–18) which have addressed this potential risk factor, all but two (16, 18) have found a positive association, and two (11, 12) have found a statistically significant association. In this paper, we report on the results of a case-control study of Alzheimer's disease which investigated a history of prior head trauma as one of four major risk factors of interest. Specifically, not only were episodes of head trauma which resulted in a loss of consciousness investigated, but we examined, as a separate group, instances in which the subject sought medical care expressly for the episode. Information was also systematically sought on the age of the subject at the time of the episode, the duration of unconsciousness, if any, and the circumstances surrounding the injury.

## Materials and Methods

### *Selection of cases*

Eligible cases were all patients in one of two clinics diagnosed as having Alzheimer's disease between January 1980 and June 1985, who were living in Washington State, and who met our study eligibility criteria. The majority (90.4 percent) were patients who sought care at the Geriatric and Family Services clinic at the University of Washington Hospital. This clinic is a geriatric psychiatric clinic which, since its inception in 1978, has become a focal point for Alzheimer's disease referrals in the Seattle area. Approximately 800 medical records from patients seen at the Geriatric and Family Services clinic were reviewed, 170 of which met our study eligibility criteria. The second source of cases was the Veterans Administration Medical Center in Seattle. This source identified another 18 eligible cases. The psychiatrists at the two clinics used the same diagnostic procedures. Most of the total eligible patients from the University of Washington Hospital came from one of three case series. First, patients diagnosed between 1980 and 1982 were part of a prospective series of patients receiving a standardized evaluation described elsewhere (19). These patients were diagnosed by a consensus group using criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (20), for primary degenerative dementia. In this series, 24 of 26 patients with Alzheimer's disease who had died and been autopsied had pathologic confirmation of their clinical diagnosis. Those patients who had died and were not autopsied or who were still alive displayed a clinical course consistent with Alzheimer's disease in ongoing follow-up studies. Between 1983 and 1985, patients were enrolled in cohort studies as part of the University of Washington's Clinical Research Center and the Alzheimer's Disease Research Center, which were the second and third sources of study cases. These patients were diagnosed using criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, for primary degenerative dementia (University of Washington Clinical Research Center and Alzheimer's Disease Research Center) and criteria outlined by the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (21) (for patients from the Alzheimer's Disease Research Center). These criteria were completed for each patient.

Study exclusionary criteria consisted of: 1) a Mini-Mental State Examination (22) score greater than 26, 2) patients in whom Parkinsonian signs developed prior to the onset of cognitive impairment, 3) persons meeting the criteria for a primary diagnosis of major affective disorder, 4) patients with hypothyroidism, and 5) persons with a history of stroke or clinical history suggestive of stroke (paralysis, hemianesthesia). The diagnostic and study exclusionary criteria were used to rule out competing causes of dementia.

Because of memory impairment and cog-

nitive dysfunction in the cases, it was necessary to obtain information from surrogate respondents. Since the spouse was considered to be the relative who would provide the most accurate information (23), selection of cases was limited to those persons who were married at the time of diagnosis and had been married for at least 10 years prior to the onset of symptoms. The source of eligible cases and their response status is shown in table 1.

### *Selection of controls*

The tendency to bring a person through certain medical channels for eventual diagnosis at a highly specialized clinic is likely to be related to the educational level and socioeconomic status of the family member accompanying the case at the time of diagnosis. It is also likely to be related to the marital status of the case. For this reason, we felt it was important for controls to be of similar educational, socioeconomic, and marital status as the cases. Therefore, our first choice of control was a friend of the case and/or case surrogate. When this was not possible, a relative of the case who was not related by blood was identified.

TABLE 1

*Eligibility and response status of Alzheimer's disease patients identified from the University of Washington and Veterans Administration Medical Center, Seattle, WA, 1980–1985*

| | No. | % |
|---|---|---|
| University of Washington (Geriatric and Family Services Clinic) | 170 | |
| Veterans Administration | 18 | |
| Total number of eligible cases | 188 | |
| Excluded from analysis because of: | | |
| Patient's refusal | 31 | 16.5 |
| Physician refusal | 3 | 1.6 |
| Lost to follow-up | 7 | 3.7 |
| Illness of spouse | 4 | 2.1 |
| Completed interview | 143 | 76.1 |
| Unable to identify a suitable control | 13 | 6.9 |
| Total matched pairs analyzed | 130 | 69.1 |

When the case surrogate was initially contacted by letter, the study description contained a section explaining that participation would also involve the identification of a control pair. The case surrogate was asked to identify a potential control before our telephone contact, which occurred 1 week after the mailing of the approach letter. At this time, information was solicited regarding a potential control. This information included a verbal reiteration, on the part of study staff, to the case surrogate, of each criterion the control was required to meet (see below), and this information was recorded on a control identification sheet to ensure control eligibility. If the case surrogate was unable to identify a control before the interview, the information was requested again immediately following the interview, and, if necessary, again in the following weeks. Control surrogates were interviewed as soon as possible following their identification by the case surrogate, this period being usually between 1 and 3 weeks. For 13 case pairs, a control was never identified; these 13 cases were excluded from further analysis after we conducted analyses which confirmed their similarity to the 130 study cases with respect to their distribution by age and their exposure frequencies for the major risk factors of interest.

In this way, case surrogates selected controls who met the following criteria for inclusion in the study: 1) the control could not be suffering from memory loss or have a history of any comorbid conditions which would have resulted in the exclusion of a potential case; 2) the control was the same sex and approximately the same age as the case (within 10 years); and 3) the control and his or her spouse had been married for at least 10 years prior to the year of onset of symptoms in the case. When two or more potential controls were available for a given case, preference was given to a control living in Washington State. Controls were also selected so that a surrogate respondent was available for interview regarding the control's history. This yielded a case pair

(Alzheimer's disease case and surrogate respondent) and a control pair (control and surrogate respondent). The spouse was always the preferred surrogate, but in 12.3 percent of the sample, the case's spouse was too ill to serve as surrogate and an adult child was selected for interview. Again in this situation, the relationship between the case and the case surrogate was matched in the control pair. For example, if a daughter of a male case was interviewed, the control surrogate was the daughter of a male control.

### *Interview*

Case and control surrogates were interviewed by telephone in 1985 using a structured, standardized questionnaire. All questions dealing with the exposures of interest were asked for the time period prior to 1 year before the case surrogate noticed the beginning of symptoms in the case. This year is referred to as the "reference year." Since onset of Alzheimer's disease is often insidious, this requirement helped to ensure the absence of symptoms at the time of exposure. Each case's matched control was assigned the same reference year in order to obtain information for a similar time frame. The interview required approximately 45 minutes to administer, and included a range of risk factors and descriptive epidemiologic and demographic data.

### *Exposure ascertainment*

To enable the study of a broad range of head injuries, we asked respondents whether the subject had sustained a head injury which 1) led him/her to visit a physician, 2) led him/her to seek hospital care, either in an emergency room (outpatient) or as an inpatient, or 3) resulted in a loss of consciousness, no matter how brief. This definition allowed us to capture head injuries of reasonable severity without recording those that were likely to have been biologically inconsequential. Injuries to the neck were not considered head injuries. For each head trauma episode reported, further detail was sought, including duration of unconsciousness, age at the time of the event, and circumstances surrounding the injury.

In addition, since alcohol use increases the risk of head injury (24), the question was asked, "Do you feel that alcohol has ever been a problem for your husband/wife/father/mother?"

### *Validation*

A subsample of the controls (24 percent) was interviewed so that the concordance between control surrogate and control responses could be assessed. These 31 controls were interviewed by telephone using the same questionnaire and reference year as was used for case and control surrogates. The control surrogate was always interviewed first. Following the completion of almost all of the case and control surrogate interviews, the validation study was conducted; therefore, controls' interviews ranged from a few weeks to a year following the control surrogates' interview.

### *Analysis*

All the analyses except initial frequency distributions were conducted maintaining the matching inherent in the study design. To test the statistical significance of case-control differences on dichotomous exposures (without adjustment for covariates), McNemar's test was used. Modeling techniques using conditional logistic regression were used to test the independent effect of a variable adjusting for several other factors, to test for effect modification by selected variables, and to test for the most appropriate form for modeling a variable, such as age. The concordance between control and control surrogate responses was analyzed using the kappa statistic (25).

## RESULTS

### *Description of study population*

There were 70 male and 60 female cases in the study. Almost 18 percent of the cases were deceased at the time of the interview, compared with only 7 percent of controls.

The age and social class distributions of the study subjects are shown in table 2. As expected, matching on age was difficult, and cases were older than controls, with the mean age of cases being 66.2 years and that of controls being 63.6 years ($p < 0.001$). Social class was calculated using the Four-Factor Index of Social Status (26). This index is categorized into five strata (I being the lowest and V being the highest socioeconomic stratum) and takes into account the education, occupation, sex, and marital status of the case or control and his or her spouse. Therefore, this variable was computed only on the 88 percent of the sample in which the spouse was the surrogate respondent. Cases and controls were similar with regard to social class ($p = 0.95$), as was expected because of the method used for matching. Cases and their spouses had been married an average of 42.6 years; controls and their spouses had been married an average of 41.2 years. Among respondents who were adult children, the average age among case respondents was 49.4 years, and among controls, it was 50.3 years.

The average Mini-Mental State Examination score among cases at diagnosis was 16.3 (of a possible 30), with a standard deviation of 7.0. The average score on the Mental Status Questionnaire (27) was 4.9 (of a possible 10), with a standard deviation of 2.9. On average, the diagnosis of Alzheimer's disease was made 5 years after onset of symptoms.

TABLE 2

*Selected demographic characteristics of 130 cases of Alzheimer's disease diagnosed at the University of Washington and at the Veterans Administration Medical Center, Seattle, WA, 1980–1985, and 130 friend and nonblood relative controls*

| | Cases | | Controls | |
|---|---|---|---|---|
| | No | % | No. | % |
| Age (years) in the reference year | | | | |
| <55 | 16 | 12.3 | 24 | 18.5 |
| 55–64 | 41 | 31.5 | 41 | 31.5 |
| 65–74 | 49 | 37.7 | 49 | 37.7 |
| ≥75 | 24 | 18.5 | 16 | 12.3 |
| Total | 130 | 100.0 | 130 | 100.0 |
| Social class* | | | | |
| I (lowest) | 5 | 4.4 | 4 | 3.5 |
| II | 14 | 12.3 | 18 | 15.8 |
| III | 24 | 21.0 | 22 | 19.3 |
| IV | 36 | 31.6 | 36 | 31.6 |
| V (highest) | 35 | 30.7 | 34 | 29.8 |
| Total | 114 | 100.0 | 114 | 100.0 |

* Excludes subjects with nonspouse respondents.

### *Head trauma regardless of status of unconsciousness*

At least one qualifying head trauma episode was reported for 23.9 percent of the cases, compared with 8.5 percent of the controls (table 3). The results for the matched analyses yielded an unadjusted odds ratio of 3.5 (95 percent confidence interval (CI) 1.6–7.7). This odds ratio remained unchanged after adjustment for age (in the reference year) and family history

TABLE 3

*Matched analysis of results for the association between an episode of head trauma and Alzheimer's disease, regardless of loss-of-consciousness status, prior to reference year,* Seattle, WA, 1980–1985*

| Cases | Controls | | Total | OR† | 95% confidence interval |
|---|---|---|---|---|---|
| | One or more episodes of head trauma | No episodes of head trauma | | | |
| One or more episodes of head trauma | 3 | 28 | 31 | 3.5 | 1.56–7.68 |
| No episodes of head trauma | 8 | 91 | 99 | | |
| Total | 11 | 119 | 130 | | |

* Year of reported onset of symptoms minus 1 year.

† OR, crude odds ratio (ratio of discordant pairs, 28/8).

of Alzheimer's disease (95 percent CI 1.5–8.3). The degree of concordance between the control's responses and the control's surrogate responses, measured by the kappa statistic, was 0.5 for all head traumas regardless of loss-of-consciousness status.

### *Multiple head injuries*

Two separate episodes of head trauma were reported for four cases, and no multiple events were reported for controls. For these cases, the results that follow were calculated using the most recent head trauma episode.

### *Head trauma stratified by presence or absence of unconsciousness*

When episodes of head trauma were stratified by whether the subject lost consciousness or not, the odds ratios (adjusted for age and family history of Alzheimer's disease) were 2.9 for events accompanied by unconsciousness and 5.5 for events with no loss of consciousness (table 4). Both of these effects were statistically significant. Although these odds ratios differed, their confidence intervals almost completely overlapped.

### *Duration of unconsciousness*

To study whether the duration of unconsciousness differed for cases versus controls, we compared the length of time cases and controls were unconscious. Duration of unconsciousness was log-transformed because of its skewed distribution. Of the 19 cases whose episode of head trauma was accompanied by a loss of consciousness, the duration of unconsciousness was known for 18. For controls, information on the duration of unconsciousness was known for all eight. A two-sample $t$ test limited to subjects with an episode of head trauma accompanied by unconsciousness (unmatched because of small numbers) showed an absolute difference but no statistical difference between the mean durations of unconsciousness in the two groups (geometric mean, 15 minutes for cases, 77 minutes for controls; $p = 0.22$). There was no difference in the odds ratio for longer versus shorter durations of unconsciousness.

### *Time since last head trauma episode*

Since the odds ratios were similar regardless of whether a loss of consciousness was involved, the remaining findings will focus on the combined data for head trauma episodes with or without loss of consciousness. The average number of years between the head trauma episode and the reference year in the cases was 21.3, with a range of 1–64 years. For controls, the average number of years was 32.5, ranging from 1 to 51 years. For cases, there was an average of 5 years between the reference year (1 year

TABLE 4

*Head trauma episodes stratified by status of consciousness for 130 Alzheimer's disease cases and 130 matched controls, Seattle, WA, 1980–1985*

| Exposure | No.* | | OR† | |
|---|---|---|---|---|
| | Cases | Controls | Unadjusted (95% CI†) | Adjusted‡ (95% CI) |
| No episodes of head trauma | 99 | 119 | 1.0 | 1.0 |
| One or more episodes of head trauma with loss of consciousness | 19 | 8 | 3.0 (1.23–7.07) | 2.9 (1.10–7.53) |
| One or more episodes of head trauma with no loss of consciousness | 12 | 3 | 5.0 (1.41–19.59) | 5.5 (1.35–22.5) |

* Number of cases and controls in each category. All odds ratios reported were calculated maintaining matching.

† OR, odds ratio; CI, confidence interval.

‡ Adjusting for age and family history of Alzheimer's disease.

TABLE 5

*Time from last head trauma episode to reference year* for 130 Alzheimer's disease cases and 130 matched controls, Seattle, WA, 1980–1985*

| Time since last head trauma episode | Prevalence (%) of exposure | | OR† | 95% confidence interval |
|---|---|---|---|---|
| | Cases | Controls | | |
| No episodes of head trauma | 76.2 | 91.5 | 1.0 | |
| ≥30 years | 6.9 | 4.6 | 1.5 | 0.44–5.17 |
| 10–29 years | 7.7 | 2.3 | 5.0 | 1.25–19.84 |
| 1–9 years | 9.2 | 1.5 | 9.7 | 1.12–83.34 |
| $p$ (test for trend) = 0.002 | | | | |

* Year of reported onset of symptoms minus 1 year.

† OR, odds ratio adjusted for age and family history of Alzheimer's disease.

before appearance of symptoms) and the year of diagnosis of disease, and the interview year was an average of 2.3 years after diagnosis.

To further examine the time since the most recent trauma, we grouped episodes into three categories: 1) 30 or more years before the reference year, 2) 10–29 years before the reference year, and 3) 1–9 years before the reference year. As table 5 shows, the results from the conditional logistic regression analysis adjusting for age and family history of Alzheimer's disease revealed that the estimated relative risk of Alzheimer's disease increased as the time between the last head trauma event and the onset of the disease diminished ($p_{trend}$ = 0.002).

There has been some concern in the literature (12) that differential recall may account for the association between head trauma and Alzheimer's disease, and that this bias could operate by case respondents' selectively recalling episodes of head trauma in the years immediately preceding the onset of symptoms in an effort to attribute the onset of disease to a specific event. At the same time, control respondents may tend to forget such events. Clearly, this does not preclude the possibility of differential recall operating throughout all years of exposure or selectively affecting the early years. To examine whether recall was biased toward *recent* events, we conducted further analyses in which any event occurring within 5 years of the reference year was excluded. This period was an average of 10 years prior to diagnosis of disease in the cases, and an average of 12.3 years prior to the interview. The overall odds ratio, adjusted for age and family history of Alzheimer's disease for this analysis, was 2.7 (95 percent CI 1.1–6.5), which can be compared with the value of 3.5 reported earlier for events including this 5-year period. For this analysis, eight of the 31 episodes reported for cases were excluded, compared with one of 11 episodes reported for controls. When this analysis was stratified by status of consciousness, the odds ratios (adjusted for age and family history of Alzheimer's disease) were 2.5 (95 percent CI 1.0–6.4) for head trauma episodes accompanied by a loss of consciousness and 3.8 (95 percent CI 0.6–23.6) for head trauma episodes without accompanying loss of consciousness. Conditional logistic regression was performed to examine the time interval (grouped into tertiles as before) between the last episode of head trauma and the reference year, excluding head injuries that occurred within 5 years of the reference year; the test for trend remained statistically significant, with $p$ = 0.006.

We found no clear differences between cases and controls in the frequencies of the different circumstances surrounding the head injury. For cases, 37 percent of the head injuries were the result of automobile-related accidents; for controls, 27 percent were from automobile-related accidents.

Injuries in other categories (domestic accidents, occupation-related accidents, recreation-related accidents, war injuries) were similar for cases and controls. Additionally, we found no differences between cases and controls in the frequency of alcohol problems (proportion in cases, 8.5 percent; proportion in controls, 10 percent), a common cause of accidents.

## Discussion

There have been eight studies published which have addressed head trauma as a risk factor for Alzheimer's disease (11–18). A summary of the results from these studies is presented in table 6. Two of these studies found a statistically significant association between head trauma and Alzheimer's disease (11, 12); all but two of the remaining studies (16, 18) found odds ratios of 2.0 or more, but not statistically significant associations. All of these studies, except the study of Heyman et al. (11), defined head trauma as an episode accompanied by a loss of consciousness.

In the study of Mortimer et al. (12), the odds ratios of 4.5 for the comparison with hospital controls and 2.8 for the comparison with neighborhood controls may be compared with the odds ratio derived in

TABLE 6

*Summary of head trauma results from other case-control studies of Alzheimer's disease*

| Authors | Type of controls | No. of cases | No. of controls | OR* | Statistical significance† | Comments |
|---|---|---|---|---|---|---|
| Heyman et al. (11) | | 40 | 80 | 5.3 | S | Neighborhood controls matched by age (±5 years), sex, and race. OR was 11.52 when education and residence were included as covariates. |
| Mortimer et al. (12) | Hospital population | 78 | 76 | 4.5 | S | All male sample. Two control groups, hospital and neighborhood, matched by age (±1 year), sex, and race. |
| | | | 48 | 2.8 | NS | |
| Chandra et al. (13) | | 64 | 64 | 6.0 | NS | Matched by age (±3 years) and race. All cases and controls selected from a single geriatric clinic. |
| Amaducci et al. (14) | Hospital population | 116 | 116 | 3.5 | NS | Two control groups; hospital and neighborhood, matched by age (±3 years), sex, and region of residence. |
| | | | 97 | 2.0 | NS | |
| Shalat et al. (15) | | 98 | 162 | 2.4 | NS | Neighborhood controls matched by year of birth, sex, and town of residence. |
| Chandra et al. (16) | | 296 | 296 | 1.2 | NS | Neighborhood controls matched by age, sex, race, and length of residence. Medical record review. |
| Ferini-Strambi et al. (17) | | 55 | 110 | 2.3 | NS | Two controls matched to each case by age, sex, residential area, and education. |
| Soininen and Heinonen (18) | | 63 | 91 | 0.6 | NS | Institutionalized cases and combination of institutionalized and general population controls, matched by age interval, sex, and duration of institutionalization. |

* OR, odds ratio, or relative odds.

† S, $p \leq 0.05$; NS, $p > 0.05$.

this study of 2.9, the risk estimate for the age- and family history-adjusted odds ratio with loss of consciousness. The odds ratio of 5.3 derived from the study of Heyman et al. (11) may be compared with the overall adjusted figure of 3.5 in this study. Despite the fact that the study of Amaducci et al. (14) failed to find a statistically significant relation between head trauma and Alzheimer's disease, the magnitude of the effect measure from that study is also comparable with the other studies, including this one. Factors that must be taken into account in the interpretation and comparison of the studies include the degree of severity of the definition of the head trauma and the limitations of the sample size to find a statistically significant effect. Furthermore, two of the studies (14, 15) excluded subjects in whom traumatic head injury occurred shortly before onset or was suspected as an underlying cause of dementia, which may have served to drive the odds ratios toward the null value.

The most widely accepted indicator of brain damage is the extent and duration of impairment of consciousness (28, 29). The present study appears to be the only one so far that has examined the duration of unconsciousness caused by the head injury. We found no clear differences between cases and controls with regard to this measure of severity. Our finding of a longer absolute duration of unconsciousness in controls is based on a small sample and is not statistically significant. However, it is possible that cases may recall a greater number of episodes, while controls recall only the most traumatic. This might also explain the higher magnitude of the adjusted odds ratio observed for head trauma with no loss of consciousness compared with that associated with head trauma accompanied by such a loss (5.5 vs. 2.9). Future case-control studies of Alzheimer's disease investigating head trauma will require larger samples to study this issue. We also found little difference between cases and controls in the manner in which the head injury occurred.

The average time between the head injury and the reference year was 21.3 years for cases and 32.5 years for controls. Mortimer et al. (12) reported an average interval between the head trauma event and the interview of 35.2 years for cases and 40.4 years for controls. Taking into account the different endpoints used in these calculations, these figures are comparable for controls, but for cases, head injuries were closer to the onset of disease symptoms in the current study than in the study by Mortimer et al. (12).

The primary concern in interpreting our results is that differential recall between case and control surrogates could account for some or all of the observed association between head trauma and Alzheimer's disease, particularly if recall bias was operating by case surrogates selectively recalling (or control surrogates selectively underrecalling) head injuries occurring shortly before the onset of disease symptoms. It should be noted, however, that recall bias could affect all years or selectively the early years of exposure. The analyses conducted to examine the time since the most recent head trauma event excluding episodes occurring within 5 years of the reference year overcome, to some extent, this potential problem. These analyses exclude any head injury that occurred an average of at least 10 years before diagnosis and an average of 12.3 years prior to the interview. Another important contribution of these analyses is that they minimize the possibility that an episode of head trauma occurred as a consequence of the symptoms of Alzheimer's disease. Although the confidence intervals for these risk estimates included 1.0, their magnitude remained similar to those odds ratios including episodes of head trauma occurring within 5 years of the reference year. The change in statistical significance is most likely due to a lack of adequate power rather than to the presence of recall bias. The persistence of the association in these analyses lends support to the head trauma hypothesis.

A meta-analysis incorporating the results

from the present study was recently presented (30). Eight studies formed the basis for this analysis, and the results revealed a summary odds ratio of 2.8 (95 percent CI 1.8–4.0). This compares well with the odds ratio in the current study of 2.9 for events of head trauma accompanied by a loss of consciousness. All of these studies have used informants for cases and controls to gather information regarding past exposures.

The kappa statistic comparing control surrogate and control responses for the composite head trauma variable in our study was 0.5. It is important to note that within the group with no agreement between control and control surrogate, the lack of agreement was solely the result of underestimation of the control's exposure; specifically, among the discordant pairs within the two-by-two table, two control surrogates reported false negatives (the surrogate reported no head trauma when the control reported one) and no surrogates reported false positive head traumas. Additionally, concordance was only studied in a subset of controls ($n = 31$), and the small sample size of this group may have resulted in an unstable kappa statistic. Future case-control studies of Alzheimer's disease would benefit from interviewing all of the controls as part of the validation study.

The hypotheses of a "threshold" of neuronal loss and damage to the blood-brain barrier offer the most plausible mechanisms by which head trauma could be of etiologic importance in the development of Alzheimer's disease (31). There is increasing evidence that there is significant redundancy in brain tissue and that neuronal systems may undergo considerable damage before clinical symptoms emerge (31). Neuronal loss increases with age (32), and it is possible that this loss may be accelerated by a head injury. Damage to the blood-brain barrier may result in increased permeability and contact with leukocytes, stimulating the immune system to specific brain antigens and producing a secondary response to such antigens (12). Increased permeability of the blood-brain barrier would also provide reduced protection to viruses and toxins such as aluminum and other potential causes or accelerators of the Alzheimer process (31, 33, 34).

Aging has also been implicated in the ability of neuronal systems to recover from structural damage (35). Therefore, the brain's ability for regrowth and reorganization may diminish with age, resulting in more devastating consequences to cognitive function from a head injury in older age. Our finding of a trend of increasing risk of Alzheimer's disease with decreasing time intervals between the head trauma event and the reference year supports such a hypothesis.

## References


1. Claude H, Cuel J. Demence pre-senile post-traumatique apres fracture de crane: considerations medico-legales. (In French). Ann Med Leg 1939;19:173–84.
2. Corsellis JAN, Brierly JB. Observations on the pathology of insidious dementia following head injury. J Ment Sci 1959;105:714–20.
3. Rudelli R, Stron JO, Welch MD, et al. Posttraumatic premature Alzheimer's disease: neuropathologic findings and pathogenetic considerations. Arch Neurol 1982;39:570–5.
4. Corsellis JAN. Posttraumatic dementia. In: Katzman R, Terry RD, Bick KL, eds. Alzheimer's disease: senile dementia and related disorders. (Aging, vol 7). New York: Raven Press, 1978:125–33.
5. Strich SJ. Diffuse degeneration of the cerebral white matter in severe dementia following head injury. J Neurol Neurosurg Psychiatry 1956;19: 163–85.
6. Roberts AH. Brain damage in boxers: a study of prevalence of traumatic encephalopathy among ex-professional boxers. London: Pitman Books Ltd, 1969.
7. Brandenburg W, Hallervorden J. Dementia pugilistica mit anatomischem Befund. (In German). Virchows Arch [A] 1954;325:680–705.
8. Grahamm H, Ule G. Beitrag zur Kenntnis der chronischen cerebralen Krankheitsbilder bei Boxern. (In German). Psychiatr Neurol 1957;134:261–83.
9. Constantinides J, Tissot R. Lesions neurofibrillaires d'Alzheimer generalisees sans plaques seniles. (In French). Arch Suisses Neurol Neurochir Psychiatr 1967;100:117–30.
10. Spillane JD. Five boxers. Br Med J 1962;2:1205–10.
11. Heyman A, Wilkinson WE, Stafford JA, et al. Alzheimer's disease: a study of the epidemiological aspects. Ann Neurol 1984;15:335–41.

12. Mortimer JA, French LR, Hutton JT, et al. Head injury as a risk factor for Alzheimer's disease. Neurology 1985;35:264–7.
13. Chandra V, Philipose V, Bell PA, et al. Case-control study of late onset "probable Alzheimer's disease." Neurology 1987;37:1295–1300.
14. Amaducci LA, Fratiglioni L, Rocca WA, et al. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of an Italian population. Neurology 1986;36:922–31.
15. Shalat SL, Seltzer B, Pidcock C, et al. Risk factors for Alzheimer's disease: a case-control study. Neurology 1987;37:1630–3.
16. Chandra V, Kokmen E, Schoenberg BS. Head trauma with loss of consciousness as a risk factor for Alzheimer's disease using prospectively collected data. (Abstract). Neurology 1987;37(suppl 1):152.
17. Ferini-Strambi L, Smirne S, Truci G, et al. Alzheimer's disease: clinical and epidemiological aspects in patients with early onset of the disease. (Abstract). Clin Neurol Neurosurg 1987;89(suppl 2):10–11.
18. Soininen H, Heinonen OP. Clinical and etiological aspects of senile dementia. Eur Neurol 1982;21: 301–410.
19. Larson EB, Reifler BV, Sumi SM, et al. Diagnostic evaluation of 200 elderly patients with suspected dementia. J Gerontol 1985;40:536–45.
20. American Psychiatric Association Task Force. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington DC: American Psychiatric Association, 1980.
21. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;4:939–44.
22. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
23. Pickle LW, Brown LM, Blot WJ. Information available from surrogate respondents in case-control interview studies. Am J Epidemiol 1983; 118:99–108.
24. Galbraith S, Murray WR, Patel AR, et al. The relationship between alcohol and head injury and its effect on the conscious level. Br J Surg 1976; 63:128–30.
25. Fleiss JL. Statistical methods for rates and proportions. New York: John Wiley & Sons, 1973.
26. Hollingshead AB. Four-factor index of social status. New Haven, CT: Yale University, Department of Sociology. (Unpublished manuscript).
27. Kahn RL, Goldfarb AI, Pollock M, et al. Brief objective measures for the determination of mental status in the aged. Am J Psychiatry 1960;117: 326–8.
28. Boll TJ. Behavioral sequelae of head injury. In: Cooper PR, ed. Head injury. Baltimore: Williams & Wilkins Co, 1982:363–75.
29. Jennett B, Teasdale G, Galbraith S, et al. Severe head injuries in three countries. J Neurol Neurosurg Psychiatry 1977;40:291–8.
30. Mortimer JA. Genetic and environmental risk factors for Alzheimer's disease: key questions and new approaches. In: Altman H, ed. Alzheimer's disease and dementia: problems, prospects, and perspectives. New York: Plenum Press (in press).
31. Mortimer JA, Pirozzolo FJ. Remote effects of head trauma. Dev Neuropsychol 1985;1:215–29.
32. Nandy K. Senile dementia: a possible immune hypothesis. In: Mortimer JA, Schuman LM. The epidemiology of dementia. New York: Oxford University Press, 1981.
33. Brody JA, Gibbs DJ. Chronic neurological diseases. In: Evans AS, ed. Viral infections of humans: epidemiology and control. New York: Plenum Medical Book Company, 1976:519–38.
34. Graves AB, White E, Koepsell T, et al. A case-control study of Alzheimer's disease. (Abstract). Am J Epidemiol 1987;126:754.
35. Giannotta SL, Weiner JM, Cerverha BB. Prognosis and outcome in severe head injury. In: Cooper PR, ed. Head injury Baltimore: Williams & Wilkins Co, 1982.